REMARKS

Summary of the Invention

The invention features methods for identifying whether test compounds that modulate the biological activity of a CeSERT have an effect on non-CeSERT, secondary targets, and for identifying test compounds that modulate the uptake of serotonin by secondary targets other than a SERT.

Summary of the Office Action

Claims 1-22 are pending in the application. Claims 1-11 are rejected under 35 U.S.C. § 112, second paragraph for lack of clarity, and under 35 U.S.C. § 112, first paragraph for introducing new matter into the application. Claims 1-22 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and for lack of enablement. By this reply Applicants amend claims 1, 2, 12, and 13, cancel claims 6 and 17, and address each of the Examiner's rejections below.

Support for the Amendments

Support for the amendment to claims 1, 2, 12, and 13 is found in the specification on, e.g., page 2, line 17, through page 3, line 11, and page 36, line 27, through page 37, line 24. No new matter is added by the amendment.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-11 are rejected under 35 U.S.C. § 112, second paragraph, for lack of clarity.

The Examiner states that claim 1 is indefinite as written, stating:

> The claim is directed to a method for determining the activity range of a test compound against a secondary target that is not a serotonin reuptake transporter (SERT). The steps of the method only result in indicating that a compound has a secondary target. It appears that the steps of the method have not met the goal of the preamble, as an activity range was not determined. (Office Action, p. 8.)

Applicants have cancelled claim 6 and have amended claim 1 so that it now recites a method for determining whether a test compound, which modulates the uptake of serotonin by a serotonin reuptake transporter (SERT), has an effect on a secondary target. The preamble of claim 1, as amended, clearly indicates that the method tests compounds that are known to modulate serotonin uptake by a SERT for their effect on a non-SERT, secondary target. The method steps involve contacting a *Caenorhabditis elegans* nematode lacking a wild-type SERT and expressing a mutant CeSERT polypeptide selected from the group consisting of a CeSERT(*n822*) polypeptide, a CeSERT(*n823*) polypeptide, and a CeSERT(*n3314*) polypeptide with a test compound and determining whether the test compound has an effect on a defined behavior of the nematode. An observed difference in a defined behavior of the nematode contacted with the test compound, relative to an equivalent nematode not contacted with the test compound, indicates that the test compound has an effect on a non-SERT, secondary target. Applicants submit that claim 1, as amended, is clear and definite. Therefore, Applicants respectfully request that the rejection of claims 1-11 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

New Matter

Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, for introducing subject

matter that was not described in the specification at the time the application was filed. The Examiner states that the specification has only provided support for test compounds that modulate the uptake of serotonin and that "[t]he specification provides no implicit or explicit support for the context of test compounds that do not modulate the uptake of serotonin" (Office Action, p. 4).

In response, Applicants have cancelled claim 6 and have amended claim 1 to recite that the test compound "modulates the uptake of serontonin by a serotonin reuptake transporter." The rejection of claims 1-11 is now moot in light of the present amendment, and Applicants respectfully request that the rejection be withdrawn.

Written Description

Claims 1-22 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states that "the instant specification has only described *C. elegans* comprising a mutated mod-5 gene comprising mod-5 (n822), mod-5 (n823), or mod-5 (n3314) mutations...[and that] the instant specification has failed to describe the other nematodes embraced by the claims" (Office Action, p. 3).

Applicants respectfully disagree, but have cancelled claims 6 and 17 and have amended claims 1, 2, 12, and 13 to recite that the nematode that is used in the method of claims 1 and 12, and claims dependent therefrom, is a *Caenorhabditis elegans* nematode that lacks a wild-type SERT polypeptide and that expresses a CeSERT polypeptide selected from the group consisting of a CeSERT(*n822*) polypeptide, a CeSERT(*n823*) polypeptide, and a CeSERT(*n3314*) polypeptide. The Examiner acknowledges that the specification "has...described *C. elegans*

comprising a mutated mod-5 gene comprising mod-5 (n822), mod-5 (n823), or mod-5 (n3314) (Office Action, p. 3). Therefore, claims 1-5, 7-16, and 18-22, as presently amended, are fully described by the specification. Accordingly, Applicants respectfully request that the rejection of claims 1-22 under 35 U.S.C. § 112, first paragraph, for lack of written description be withdrawn.

Enablement

Claims 1-22 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that "the instant specification has provided guidance for use of C. elegans mutants mod-5 (n822), mod-5 (n823) or mod-5 (n3314) but the instant specification has failed to provide guidance for use of other nematodes embraced by the claims" (Office Action, p. 6).

As is discussed above, claims 6 and 17 have been cancelled and independent claims 1 and 12 have been amended to recite that the nematode is a *Caenorhabditis elegans* nematode that lacks a wild-type SERT and that expresses a mutated CeSERT selected from the group consisting of a CeSERT(*n822*) polypeptide, a CeSERT(*n823*) polypeptide, and a CeSERT(*n3314*) polypeptide. Because the method of claims 1 and 12, as amended, utilize a *C. elegans* nematode that does not express a fully functional, wild-type SERT, an observed effect of the test compound on the defined behavior of the nematode can be attributed to the modulation of a secondary target. Therefore, the Examiner's argument that the method of claims 1 and 12 would not distinguish between the modulation of a wild-type SERT and the modulation of a secondary target is moot in light of the present amendment to claims 1 and 12.

The Examiner also argues that claims 1-22, as written, lack enablement because:

> the claims as written are broad as they encompass any defined behavior and any secondary target. The claims (1-22), as written fail to provide a correlation

> between defined behaviors and serotonin. In addition, the claims (1-11) fail to provide a nexus between modulation of the secondary target and serotonin uptake. Such a nexus appears to be important as the role of the secondary target appears to promote serotonin uptake by circumventing the defective CeSERT. Finally, given the breadth of the claims directed to any nematode expressing a mutated CeSERT, it would appear that such nematode comprises wild-type SERTs in addition to the mutated CeSERT...Therefore, the uptake of serotonin is normal and unaffected by the expression of mutated CeSERT in the nematodes...Given the language of the claims, the evidence of record has failed to provide guidance for distinguishing modulation of a SERT as opposed to a secondary target in the presence of a test compound. As such, the claims as written are not enabled. (Office Action, pp. 7-8.)

Applicants respectfully disagree.

Present Claims 1-5 and 7-11 Do Not Lack Enablement

Independent claim 1, as amended, recites a method for determining whether a test compound that is known to modulate serotonin reuptake by a SERT has an effect on a secondary target as determined by observing a change in a defined behavior of a nematode that lacks expression of a wild-type SERT polypeptide and that expresses a CeSERT polypeptide selected from the group consisting of a CeSERT(*n822*) polypeptide, a CeSERT(*n823*) polypeptide, and a CeSERT(*n3314*) polypeptide relative to an equivalent nematode that is not contacted with the test compound. In other words, the method of claim 1 can be used to identify compounds that produce undesirable side effects due to their interaction with a non-CeSERT, secondary target. The specification teaches that several defined behaviors, such as movement (e.g., swimming behavior), nose contraction, egg-laying, pharyngeal pumping, and defecation, or the rate at which those behaviors occur, can be monitored in *C. elegans* nematodes and that many of these defined behaviors are serotonin-independent and result from interaction with a non-CeSERT, secondary

target (see, e.g., page 10, lines 22-27, page 28, line 22, through page 33, line 20, and page 37, lines 15-19).

As an example of the method of present claims 1-5 and 7-11, the specification describes contacting wild-type nematodes and nematodes expressing a defective CeSERT polypeptide with fluoxetine, which is a SERT inhibitor that blocks serotonin uptake by serotonergic neurons. In the presence of varying concentrations of fluoxetine, both the wild-type and CeSERT-defective nematodes displayed several defined behaviors, including, e.g., paralysis, nose muscle contraction, and egg-laying (see, e.g., page 30, line 25, through page 35, line 20). The specification states that these behaviors result through activation of a CeSERT-independent, serotonin-independent pathway. Therefore, the presence of these behaviors in both groups of nematodes, upon contact of the nematodes with fluoxetine, clearly indicates that fluoxetine acts on a target other than a CeSERT (i.e., a secondary target). This is consistent with the well known broad range of side effects experienced by patients taking fluoxetine; side effects those involved in drug discovery seek to avoid.

As is summarized above, the specification clearly demonstrates that the skilled artisan can distinguish between the modulation of a SERT and a secondary target in the presence of a test compound by observing a defined behavior of a nematode. Accordingly, the method of present claim 1, and claims dependent therefrom, do not lack enablement, and Applicants respectfully request that the rejection of claims 1-11 under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn

Present Claims 12-22 Do Not Lack Enablement

Independent claim 12, as amended, recites a method for identifying a test compound that modulates serotonin reuptake by acting on a non-SERT, secondary target. The method of present claims 12-16 and 18-22 involves identifying a change in a defined behavior of a nematode that lacks expression of a wild-type SERT polypeptide and that expresses a CeSERT polypeptide selected from the group consisting of a CeSERT(*n822*) polypeptide, a CeSERT(*n823*) polypeptide, and a CeSERT(*n3314*) polypeptide when that nematode is contacted with a test compound relative to the defined behavior of an equivalent nematode that is not contacted with the test compound. A change in the defined behavior of the test nematode relative to the control nematode indicates that the test compound modulates the level of serotonin at the synapse (e.g., by either increasing or decreasing serotonin reuptake) by acting on a non-CeSERT, secondary target. As is discussed above, the specification discloses several defined behaviors, such as movement (e.g., swimming behavior), nose contraction, egg-laying, pharyngeal pumping, and defecation, or the rate at which those behaviors occur, that can be monitored in *C. elegans* nematodes (see, e.g., page 10, lines 22-27).

As an example of the method of present claims 12-16 and 18-22, the specification teaches that food-deprived nematodes expressing a wild-type CeSERT slow their locomotory rate slightly in response to a food source (e.g., bacteria), whereas food-deprived nematodes defective in serotonin reuptake due to the expression of a mutated CeSERT polypeptide exhibit a hyperenhanced slowing response when exposed to bacteria (see, e.g., page 21, lines 7-28). The specification states that this behavior is CeSERT- and serotonin-dependent, and is a consequence of a defect in the clearing of serotonin from the relevant synapses (see page 21, lines 24-28).

Therefore, the loss of the hyperenhanced slowing response as a result of contacting a nematode expressing a defective CeSERT polypeptide with a test compound, relative to a nematode expressing a defective CeSERT polypeptide but not contacted with the test compound, would indicate that the test compound promotes an increase in serotonin reuptake by modulating the activity of a non-CeSERT, secondary target, thereby circumventing the serotonin reuptake defect associated with the mutated CeSERT polypeptide. Alternatively, an increase in the hyperenhanced slowing response as a result of contacting a nematode expressing a defective CeSERT polypeptide with a test compound, relative to a nematode expressing a defective CeSERT polypeptide but not contacted with the test compound, indicates that the test compound modulates the activity of a non-CeSERT, secondary target by promoting a decrease in serotonin reuptake. Therefore, the specification clearly provides considerable guidance that would enable the skilled artisan to identify test compounds that modulate serotonin uptake by acting through a non-CeSERT, secondary target by simply allowing the skilled artisan to observe a change in a defined behavior of a nematode expressing a mutated CeSERT polypeptide following its contact with a test compound. Accordingly, the skilled artisan can practice the full scope of claims 12-22. For this reason, Applicants respectfully request that the rejection of claims 12-22 under 35 U.S.C. § 112, first paragraph, for lack of enablement be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying for three months, to and including July 13, 2004, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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